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## New concepts in axillary management of breast cancer

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## Abstract

In the last decades, surgical treatment of breast cancer has evolved from more extensive procedures like radical mastectomy to less invasive breast conserving surgery. Similarly, surgical management of axilla has enormously changed from routine axillary dissection to sentinel lymph node biopsy. Traditional surgical approach to the axilla in case of sentinel lymph node negativity is to avoid completion axillary dissection. However, surgeons even avoid performing axillary dissection in selected patients with positive sentinel lymph node in clinical practice depending on the recent randomized controlled studies supporting this concept. All of the recent changes in the management of positive axilla necessitate surgeons to refresh their knowledge on this challenging topic.

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**Key words:** Breast; Cancer; Axilla; Sentinel lymph node

**Core tip:** In the last decades, surgical treatment of breast cancer has evolved from more extensive procedures like radical mastectomy to less invasive breast conserving surgery. Similarly, surgical management of axilla has enormously changed from routine axillary dissection to sentinel lymph node biopsy. Traditional surgical approach to the axilla in case of sentinel lymph

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## INTRODUCTION

In the last decades, surgical treatment of breast cancer has evolved from more extensive procedures like radical mastectomy to less invasive breast conserving surgery. Similarly, surgical management of axilla has enormously changed from routine axillary dissection to sentinel lymph node biopsy (SLNB). Introduction of modern imaging modalities and the increase in public awareness about breast cancer resulted in higher number of early breast cancer cases. This achievement helped more conservative surgical methods to overwhelm classic radical procedures in clinical practice. In addition, patients' preferences towards less invasive surgery and better cosmetic outcome forced surgeons to develop new surgical techniques to satisfy the patients' desires.

Currently, axillary dissection is not performed in patients with negative SLNB. On the other hand, traditional surgical approach to the axilla in case of SLNB positivity is to perform completion axillary dissection. However, surgeons avoid performing axillary dissection in selected patients in clinical practice. In addition, recent studies suggest that application of radiotherapy including the axillary field may be an alternative to axillary dissection

in the near future. Recent changes in the management of positive axilla necessitate surgeons to refresh their knowledge on this challenging topic.

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## SENTINEL LYMPH NODE BIOPSY

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Sentinel lymph node biopsy concept has evolved to avoid unnecessary regional lymph node dissections in most probably tumor-free lymph node regions. This technique is based on the excision and pathological examination of sentinel lymph node(s) which is assumed to be the first lymph node(s) draining the primary tumor. Sentinel lymph node biopsy was first introduced into the treatment of penile cancer and malignant melanoma and feasibility of SLNB was later proven in breast cancer<sup>[1]</sup>. In recent years, SLNB has largely replaced axillary dissection in the surgical treatment of breast cancer patients. Morbidity observed after axillary dissection such as seroma and hematoma formation, paresthesia, pain, lymph edema, restricted arm and shoulder function decreased in 6%-30% of patients treated with SLNB. Sentinel lymph node biopsy is primarily indicated in patients with clinically and radiologically normal axilla. Sentinel lymph node biopsy is a safe and accurate procedure to detect malignant cells in regional lymph nodes. However, 5%-10% false negativity rate in breast cancer has been disputed over the years, but this rate has definitely decreased to less than 5% in experienced centers. Sentinel lymph node biopsy can be performed using a blue dye and/or radiocolloid<sup>[2,3]</sup>. Combined method increases the accuracy of sentinel lymph node detection and decreases the false negativity rate, especially during the learning stage of the procedure. Patent blue, isosulfan blue, and methylene blue are the agents used as blue dyes. On the other hand, technetium labelled sulfur colloid and albumin are utilized as radioactive agents.

Sentinel lymph node biopsy can be performed in almost all patients with few exceptions. Presence of a clinically and radiologically suspicious lymph node in the axilla is an absolute contraindication. Ultrasound guided fine needle aspiration biopsy should be performed in such patients in order to exclude axillary lymph node metastases. After a negative biopsy result, caution must be taken during SLNB. Any macroscopic lymph nodes should be excised even though they do not take up blue dye or radiocolloid.

Although they cannot be predicted before the procedure, allergic reactions to either blue dye or radiocolloid could be another contraindication to SLNB. Any cross-reactivity between the dyes and/or radiocolloid or drugs with similar chemical structure was not reported. Preoperative use of anti-allergic drugs does not prevent anaphylactic reactions, however, may decrease the severity of allergic reaction. In addition, administration of any blue dye during pregnancy and lactation is not accepted as a safe procedure. In contrast, radiocolloids can be safely utilized during pregnancy as the calculated fetal dose is low.

Previous surgery to the breast and axilla is a relative contraindication for SLNB. Surgical diagnostic method is extremely important for breast cancer patients. Core needle biopsy, especially under radiologic guidance, is the preferred method for diagnosis. Surgical open biopsies such as incisional or excisional biopsy affect further breast conserving and axillary surgery. False negativity rates of SLNB after excisional biopsy may increase and periareolar subdermal injections of blue dye and radiocolloid instead of peritumoral injections increase the success rate of this procedure. However, previous axillary surgery definitely increases the false negativity in SLNB<sup>[4]</sup>. When SLNB is performed in patients with previous excisional biopsy or axillary surgery, the results should be carefully assessed.

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## NEW DEFINITIONS IN NODAL STAGING

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After the introduction of SLNB in the axillary management of breast cancer, new concepts have been introduced into the nodal staging of breast cancer<sup>[5]</sup>. Isolated tumor cells and micrometastases were the new definitions for nodal staging in addition to macrometastases. Isolated tumor cells were defined as cell clusters less than 0.2 mm in diameter or tumor cells fewer than 200 in number. On the other hand, micrometastases refer to malignant cell clusters between 0.2-2 mm in size or cells more than 200 in number. When the size of metastases is more than 2 mm, it is called as macrometastases. Presence of isolated tumor cells in an axillary lymph node is staged as N0 whereas micrometastases and macrometastases were accepted as N1. In addition, detection method of axillary metastases affects nodal staging and determines the significance of axillary metastases. Nodal metastases detected by either immunohistochemistry or molecular methods such as polymerase chain reaction are staged as N0 (i+ or mol+). Clinical significance and impact on survival of metastases detected by immunohistochemistry or polymerase chain reaction is less important compared to metastases seen on hematoxylin-eosin sections.

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## AXILLARY MANAGEMENT IN CASE OF SENTINEL LYMPH NODE NEGATIVITY

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The histopathologic examination result of SLNB determines the surgical approach to axillary lymph node basin. Main objective of SLNB is to prove that clinically and radiologically negative axilla is actually tumor-free after histopathologic examination. Previous prospective randomized studies reported false negativity rates of < 10% with SLNB<sup>[6]</sup>. These results encouraged the surgeons not to perform axillary dissection in cases with negative SLNB. Without axillary dissection, detected loco-regional recurrences were much less than the predicted ones in patients with long term follow-up possibly due to beneficial effects of adjuvant radiotherapy and systemic treatment. Five-year axillary recurrence rate changes be-

tween 0.5%-1.5% in patients with negative SLNB<sup>[7-9]</sup>. Axillary recurrence rates continued to be low even after ten years<sup>[10]</sup>. In a meta-analysis of 48 studies including 14959 patients, axillary recurrence rate was reported as 0.3% after a median follow-up time of 34 mo<sup>[11]</sup>. According to the results of previously mentioned studies, currently, axillary dissection is not performed in patients with a negative SLNB result to avoid possible morbidity due to dissection.

## AXILLARY MANAGEMENT IN CASE OF SENTINEL LYMPH NODE POSITIVITY

On the other hand, axillary lymph node dissection has been the standard of care for patients with a positive sentinel lymph node. However, a meta-analysis including 8059 patients with a positive axilla from 69 trials reported that a sentinel lymph node is the only involved node in 40%-60% of cases<sup>[12]</sup>. Frequency of non-sentinel lymph node positivity was dependent on tumor burden in sentinel lymph node and the detection method of metastases<sup>[12,13]</sup>. Tumor size (> 2 cm), macrometastases (> 2 mm) and extracapsular extension in sentinel lymph node, number (> 1) and ratio (> 50%) of positive sentinel lymph nodes and lymphovascular invasion determine the probability of metastases in non-sentinel lymph nodes<sup>[14]</sup>. Thus, axillary lymph node dissection in case of a positive sentinel lymph node has been questioned in recent studies. As a result, detection of isolated tumor cells or micrometastasis in sentinel lymph nodes is not accepted as a definite indication for axillary dissection. Even in case of macrometastasis in the sentinel lymph node, axillary lymph node dissection can be avoided in selected patients according to the results of recent studies.

Studies based on breast cancer patients' information from large data bases support this trend in daily practice<sup>[15,16]</sup>. Axillary dissection is omitted in 16.4%-20.8% of the patients with sentinel lymph node positivity<sup>[15,16]</sup>. In retrospective studies, older age, severe comorbidities, smaller tumor size, low grade, and hormone receptor positivity were reported as the most frequent reasons for avoiding axillary dissection<sup>[15,17]</sup>. Besides, higher number of removed sentinel lymph nodes, lower percentage of positive sentinel lymph nodes and pathologic N stage support the decision on only SLNB<sup>[18]</sup>. In addition, surgeons feel reluctant to perform axillary dissection when metastases in the sentinel lymph nodes were identified postoperatively. Low axillary recurrence rates reported in retrospective studies encouraged the surgeons not to perform completion axillary dissection<sup>[18-21]</sup>.

Presence of metastases in the remaining axilla in only 40%-60% of patients led to the development of nomograms to predict the patients with further metastases in the axilla<sup>[12]</sup>. However, low sensitivity, specificity, and predictive values of these nomograms raised concerns about their use in clinical practice. Since each of these nomograms was developed according to the properties of the related patient population, applicability of the results to

every patient may be misleading. Besides, all of the tumor and sentinel lymph node characteristics utilized in nomograms may be unavailable during SLNB. This might challenge the surgeon's decision to proceed with or avoid axillary dissection during surgery.

In addition, results of the recent studies questioned the necessity of completion axillary dissection after positive SLNB. Several meta-analysis reported acceptably low axillary recurrence rates without any dissection in the axilla. Sentinel lymph node positivity should be categorized according to metastatic tumor load to definitely determine the risk of axillary recurrence. Recurrence rate is expected to be different for isolated tumor cells, micrometastases, and macrometastases.

## ISOLATED TUMOR CELLS/ MICROMETASTASES AND AXILLARY DISSECTION

Surgeons first started to avoid axillary dissection in patients with isolated tumor cells or micrometastasis in sentinel lymph nodes. Primarily, patients with favorable tumor characteristics such as smaller tumor size and lower grade were selected. In a meta-analysis, 30 studies including patients with positive SLNB and without completion axillary dissection were reviewed<sup>[22]</sup>. In these studies, 3468 patients with micrometastatic disease in SLNB were included. After a median follow-up time of 42 mo, only 0.3% of the patients developed an axillary recurrence. Another study including patients from Surveillance, Epidemiology, and End Results database reported even less regional recurrence rate of 0.1% among 1767 patients with micrometastatic disease and no further axillary dissection<sup>[16]</sup>. Bilimoria *et al*<sup>[15]</sup> evaluating the patients in the United States National Cancer Data Base reported an axillary recurrence rate of 0.6% in 530 patients with micrometastatic disease. On the other hand, axillary recurrence rate was reported as less than 1% after completion axillary dissection which is similar to the rates without completion axillary dissection<sup>[7,15]</sup>.

These results from the evaluation of various data bases led to the planning of randomized controlled studies to test the role of axillary dissection in patients with micrometastases in sentinel lymph nodes. IBCSG 23-01 study randomized 931 patients with micrometastases to either axillary dissection or no further surgical treatment. Disease-free and overall survival results were similar in both groups after a median five year follow-up<sup>[23]</sup>. Patients treated with breast conserving surgery received radiotherapy whereas almost all patients were treated with systemic therapy, mostly hormonal treatment, in this study<sup>[23]</sup>. In contrast, another study evaluating patients with isolated tumor cells and micrometastases in Netherlands Cancer Registry reported a significantly higher rate of regional recurrence for patients with micrometastases and without axillary dissection<sup>[24,25]</sup>. More regional recurrences were detected especially in patients with shorter doubling time,

grade 3 tumors, and hormone receptor negativity<sup>[24,25]</sup>. As a result of these studies, surgeons avoid completion axillary dissection in patients with isolated tumor cells and micrometastases in sentinel lymph nodes.

## MACROMETASTASES AND AXILLARY DISSECTION

A meta-analysis reviewed 16 studies including 3268 patients with macrometastases in the axillary lymph nodes without completion axillary dissection<sup>[22]</sup>. These patients were followed-up for a median duration of 43 mo. Overall, axillary recurrence was detected in only 0.7% of the patients. Type of surgery and application of adjuvant radiotherapy were not clearly reported in the relevant studies. These retrospective data encouraged surgeons to design randomized controlled studies on this issue.

There was a need for a randomized controlled trial to demonstrate the requirement for completion axillary dissection in case of sentinel lymph node positivity. ACOSOG Z0011 trial is the only randomized controlled trial comparing completion axillary dissection following SLNB and SLNB alone in axilla positive breast cancer patients. Although the study was closed earlier than expected with less patient accrual than initially planned, the results of this study certainly changed daily surgical practice. Patients with T1/T2 tumors, treated with breast conserving surgery, and with 1 or 2 positive sentinel lymph nodes were included in the study. Six hundred patients were randomized into two groups and disease-free and overall survivals of the patients were compared. Almost all of the patients (96%-97%) received adjuvant chemo- and radiotherapy. After a median follow-up of 6.3 years, no significant difference was reported between the two groups concerning disease-free and overall survival rates<sup>[26]</sup>.

Presence of axillary metastases determines the adjuvant treatment protocols in breast cancer patients. Detection of metastases in axillary lymph nodes generally is an indication for chemotherapy. Adjuvant systemic treatment affects the axillary metastases as observed in the neoadjuvant setting. Completion axillary dissection following sentinel lymph node positivity helps better staging of the patient and may be therapeutic. In addition, presence of further metastases in the remaining axilla will change decision on systemic chemotherapy. On the other hand, information obtained after completion axillary dissection such as the number of involved lymph nodes may affect the decision on adjuvant radiotherapy. Involvement of four or more lymph nodes requires adjuvant radiotherapy to supraclavicular and infraclavicular lymph nodes. Besides, patients treated with breast conserving surgery will receive adjuvant radiotherapy to the remaining breast tissue and axilla will be involved in the tangential field. Adjuvant chemotherapy and radiotherapy definitely have a role in the low recurrence rates detected in the axilla even after sentinel lymph node positivity without further dissection.

## ALTERNATIVE APPROACHES TO AXILLARY DISSECTION IN POSITIVE AXILLA

Axillary dissection is the primary method used to obtain loco-regional control in breast cancer patients. Radiotherapy could be an alternative to dissection for controlling loco-regional disease in case of sentinel lymph node positivity. Previous randomized controlled studies reported non-significant differences between axillary dissection and radiotherapy to the axilla<sup>[27-29]</sup>. Recently, axillary dissection and radiotherapy were compared in a randomized controlled study regarding efficacy in loco-regional control and decreasing morbidity in patients with positive sentinel lymph node<sup>[30]</sup>. Patients with tumors 0.5 to 3 cm in size and clinically negative axilla were initially treated with SLNB. Patients with positive axilla after SLNB were randomized to either axillary dissection or axillary radiotherapy. Although the final results of the study in detail were not published, two treatment modalities seemed comparable.

## CONCLUSION

The pathologic status of the axilla has a diminishing effect on the choice of adjuvant treatments. Sentinel lymph node biopsy supplies the necessary information to decide on the adjuvant treatments. Recently, presence of axillary lymph node metastases is not accepted as an absolute indication for adjuvant chemotherapy in breast cancer. Patients with smaller tumor size and favorable prognostic factors such as hormone receptor positivity, low grade and Ki-67 expression, absence of lymphovascular invasion may be spared adjuvant chemotherapy. On the other hand, prognostic factors determining the indications for adjuvant radiotherapy may require information about the remaining axilla in case of sentinel lymph node positivity. Although adjuvant radiotherapy was applied to patients with 1 to 3 metastatic lymph nodes in certain cancer centers, four or more positive nodes are accepted as a widely used indication in treatment. Completion axillary dissection can provide further information about the axilla in case of positive sentinel lymph nodes to assist on the decision of adjuvant radiotherapy. However, radiotherapy to axilla may replace axillary dissection if further randomized controlled studies report equal efficacy between the two treatment modalities.

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